## REMARKS

The Examiner is thanked for the courtesy he extended in the interview with Applicants on October 14, 2003. All publications cited herein and not previously provided to the Examiner will be submitted under a separate cover.

The instant Application was filed on January 17, 2002, with 22 claims, four of which are independent (claims 1, 15, 18, and 20). The United States Patent and Trademark Office issued a Restriction Requirement on February 12, 2003. In response to the Restriction Requirement, Applicants elected with traverse to pursue claims 1-14 and 19 (Group I).

With this Response, Applicants have added new claims 23-109, and has canceled without prejudice non-elected claims 15-18, 20-22. Applicants have not canceled the non-elected claims for any reason related to patentability, and Applicants reserve the right to pursue these claims at a latter date in this application or in a related application. Entry of these new claims is hereby requested. No new matter has been added. Support for new claims 23-109 can be found throughout the originally filed application, including the claims, drawings, and examples. Without limitation, exemplary instances of support in the originally filed specification for particular new claims include the following: claims 23-25, (page 17, lines 6-9, page 26, lines 24-28[1], Example 6, and originally filed claim 1); claim 26 (page 10, lines 5-6; page 12, line 16-25); claims 27 and 28 (Example 5); claim 29 (Example 9); claim 30 (page 22, line 6-15); claim 30 (claim 10); claims 31-33 (Example 6, Figures 13-16); claim 35 (page 21, lines 1-19); claim 36(page 21, line 22 to page 22, line 5); claim 37 (page 22, lines 15-18); claim 38 (page 19, line

[1] stating: "In particularly preferred embodiments, the CH1 domain is deleted and the carboxyl end of the binding domain, or where the binding domain comprises two immunoglobulin variable region polypeptides, the second (*i.e.*, more proximal to the C-terminus) variable region is joined to the amino terminus of CH2 through the hinge region."

22 to page 20, line 29); claim 62 (page 22, line 20-21); claim 65-66 (page 23 lines 8-11); claim 68-69 (page 24 lines 22-25); claim 70-71 (page 24, lines 6-13); claim 72 (page 22, lines 20-21); claim 73 (page 24, lines 21-22; line page 23, lines 29-30); claim 74-76 (page 24, lines 9-13[2]); claims 77-80 (page 23, lines 8-22); claim 81 (page 23, lines 29-30); claim 82 (page 23 lines 8-22); claim 83 (page 23 lines 29-30); claim 84 (page 22, lines 20-21); claims 85-91 (page 22, line 25 to page 23, line 10)[3]; claims 90-91 (page 23, lines 1-5); claims 92-97 (page 11, lines 20-24); claim 98-101 (in Example 5 page 72, lines 21-22[4], Figure 11, page 72, and lines 29-31[5]); claims 102-106 (in Example 8 on page 75, line 12); claims 107-108 (page 16, lines 5-15)[6] ; and claim 109 (claim 19, page 57, lines 3-23, and page 12, lines 6-18).

**Objections to the Specification**

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[2] stating: "Similarly, in certain other embodiments of the invention, the binding domain-immunoglobulin fusion protein comprises a binding domain polypeptide that is fused to an immunoglobulin hinge region polypeptide comprising a mutated hinge region polypeptide in which the number of cysteine residues is reduced by amino acid substitution or deletion."

[3] stating: "Accordingly, an immunoglobulin hinge region polypeptide may be derived from, or may be a portion or fragment of (*i.e.*, one or more amino acids in peptide linkage, typically 5-65 amino acids, preferably 10-50, more preferably 15-35, still more preferably 18-32, still more preferably 20-30, still more preferably 21, 22, 23, 24, 25, 26, 27, 28 or 29 amino acids)"

[4] "The 2H7 scFv (see Example 1) was linked to the human IgG1 Fc domain via an altered hinge domain (see Figure 11). Cysteine residues in the hinge region were substituted with serine residues by site-directed mutagenesis and other methods known in the art." CytoxB MHMGIC has 3 cysteines substituted with serine.

[5] stating: "In this example, the leucine residue 234 known in the art to be important to Fc receptor binding, was mutated in the 2H7 scFv fusion protein, CytoxB-[MG1H/MG1C]."

[6] stating: "The fusion proteins of the present invention are preferably single polypeptide chains that comprise, in pertinent part, the following fused domains: a binding domain polypeptide, an immunoglobulin hinge region polypeptide, an immunoglobulin heavy chain CH2 constant region polypeptide, and an immunoglobulin heavy chain CH3 constant region polypeptide. In particularly preferred embodiments, the polypeptide domains of which the binding domain-immunoglobulin fusion protein is comprised are, or are derived from, polypeptides that are the products of human gene sequences, but the invention need not be so limited and may in fact relate to binding domain-immunoglobulin fusion proteins as provided

The Examiner objected to the Specification based on several alleged informalities unrelated to the patentability of the claimed inventions (May 22, 2003 Office Action, pages 2-3). In response to these perceived informalities, Applicants are submitting herewith a substitute Specification in compliance with § 1.125(b), including a clean version and a marked-up version (shown by brackets for deleted matter and underlining for added matter). In addition to the correction of typographical errors and the insertion of SEQ ID NO numerals noted above, the first line of the Specification has been updated to identify the provisional application from which the instant application takes priority, the embedded hyperlink and/or other form of browser executable code has been removed, and Figures 1, 6 and 19 have been renumbered to Figure 1A and B, Figure 6A and B, and Figure 19A, B, and C. No new matter has been added to the substitute Specification. Applicants request that the objections to the Specification be reconsidered and withdrawn.

**35 U.S.C. §112, Second Paragraph**

Claims 1-14 and 19 were rejected under 35 U.S.C. §112, second paragraph (May 22, 2003 Office Action, pages 3-4). The Examiner alleged that the word "derived" in claims 1, 4, 6, and 7 may not have "a universally accepted meaning" and asserted that:

> it is not clear whether the "derived" hinge is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or by altering the amino acid sequence, for examples [May 22, 2003 Office Action, page 3].

The claims are not indefinite, and Applicants traverse this rejection and respectfully request that this rejection be reconsidered and withdrawn.

The second paragraph of 35 U.S.C. §112 requires that a specification include claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards

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herein that are derived from any natural or artificial source, including genetically engineered

as his invention." Definiteness is a question of law, *Carl Zeiss Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1181, 20 USPQ2d 1094, 1101 (Fed. Cir. 1991), and determining whether a claim meets 35 U.S.C. §112, second paragraph, requires an analysis of "whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Exxon Research and Engineering Co. v. U.S.*, 60 USPQ2d 1272 (Fed. Cir. 2001); *Miles Lab., Inc. v. Shandon Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993), *cert. denied*, 114 S. Ct. 943 (1994); *In re Borkowski*, 442 F.2d 904, 909, 164 USPQ 642, 645-46 (CCPA 1970). Under the law, "If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, [section] 112 demands no more." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). So it is with the instant case. Whether considered alone or in light of the teachings of the specification, one of ordinary skill in the art can readily understand the metes and bounds of the claimed invention, and the claims are not lacking in legally required clarity.

For example, the term "derived" is used in numerous places in the Specification to refer to a polypeptide that has certain amino acid differences or changes in comparison to a naturally-occurring polypeptide containing cysteine residues. Such changes may be made, for example, by altering a polynucleotide sequence that encodes the polypeptide. See, for example, Example 5 on page 72, which describes one embodiment having a "mutant" hinge region in which all three cysteines found in a wild type hinge (of which the "mutant" hinge region may thus be referred to as a derivative) have been changed to serines using site-directed mutagenesis. Note also, for example, the following paragraph that bridges pages 24 and 25 of the Specification:

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and/or mutated polypeptides."

> In certain preferred embodiments, the mutated hinge region polypeptide is derived from a human IgG1 wild-type hinge region polypeptide. By way of example, a mutated hinge region polypeptide derived from a human IgG1 wild-type hinge region polypeptide may comprise mutations at two of the three cysteine residues in the wild-type immunoglobulin hinge region, or mutations at all three cysteine residues. . . . The cysteine residues that are present in a wild-type immunoglobulin hinge region and that are removed by mutagenesis according to particularly preferred embodiments of the present invention include cysteine residues that form, or that are capable of forming, interchain disulfide bonds.

Reference to "derived" in claims 1, 4, 6, and 7 is simply an indication of the number of cysteine residues in a hinge region polypeptide of the claimed construct in comparison to the number of cysteine residues in a related wild-type hinge region polypeptide. There is no reference in claims 1, 4, 6, and 7 to a hinge "formed by the attachment of a detectable marker, therapeutic molecule, [or] some other molecule to a hinge region." The metes and bounds of the claims are clear and understandable on their face.

Although it is the law that claims may use language that those skilled in the art understand without the need for explicit, detailed definitions in the written description, *see*, *e.g.*, *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58, 220 USPQ 303, 315-16 (Fed. Cir. 1983), such detail is provided in the instant Specification. In view of the foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

**35 U.S.C. §112, First Paragraph**

Claims 3 and 14 were rejected under 35 U.S.C. §112, first paragraph (May 22, 2003 Office Action, pages 4-6). The Examiner alleged that "the specification does not enable a binding domain with only a heavy or light chain." Applicants do not acknowledge the validity of this rejection but, for the sole purpose of expediting prosecution of the remaining claims, have

canceled these claims without prejudice. Applicants reserve the right to pursue these claims at a later date in this or a related application.

Applicants request that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

**35 U.S.C. §102**

***The First Rejection***

Claims 1-3, 5, 7-11, and 19 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Shan *et al.* (May 22, 2003 Office Action, pages 6-7). The Examiner alleged that Shan *et al.* provides "a scFv that binds CD20 that has the recited linker and the scFv is fused to a hinge that has the cysteines removed and it can not dimerize and the hinge is fused to a CH2 and CH3 and since the fusion protein has the hinge, CH2 and CH3 it is inherent that the protein has complement fixation or dependent cell-mediated cytotoxicity" (May 22, 2003 Office Action, page 7).

The Shan *et al.* article, published in 1999, was co-authored by named inventors of the instant Application. It reports the construction of four scFv constructs using nucleic acid constructs encoding the heavy and light chain variable regions from a murine anti-human CD20 monoclonal antibody called 1F5. According to the Abstract, each of the scFv constructs was joined to a derivative of human IgG1 (hinge plus CH2 plus CH3) "to facilitate purification using staphylococcal protein A."

The authors state that the goal of their work was to carry out "a series of investigations aimed at developing superior anti-CD20 Abs by cloning and modifying the Ag-combining portion of the 1F5 mAb", *i.e.*, the scFv section of the construct responsible for binding antigen (col. 1, page 6589; emphasis added). Specifically, the authors refer to studies in which they

examined the impact of the length of the linker between scFv variable heavy and light chains on binding function. Thus, at page 6589, col. 2, the authors state that, in order "to assess the relative merits of scFvs compared with intact anti-CD20 Abs," they

> constructed four scFv-Ig fusion proteins of the anti-CD20 mAb 1F5 using amino acid linkers of 0, 5, 10, and 15 residues, respectively. The properties of these scFv-Ig were then investigated.[7]

Following labeling of the "1F5 scFv-Ig" with $Na^{125}I$ by the iodogen method, cell binding assays were performed and binding activity was evaluated by ELISA and flow cytometry, and a Scatchard analysis of binding carried out (col. 2, page 6590). The authors reported that CD20 binding activity of the 1F5 scFv-Ig constructs was strongly influenced by the length of the linker (col. 1, page 6593).

Despite the fact that ADCC and complement fixation assays were known in the art at the time, the only functional activity investigated other than binding of the 1F5 scFv-Ig constructs was induction of "apoptosis of Ramos cells after cross-linking CD20 with 1F5 scFv-Ig plus GAH [goat anti-human IgG]" (col. 1, page 6593). The article states that "1F5 scFv-Ig could induce a small amount of apoptosis in Ramos cells when used alone [], but was more effective at inducing apoptosis when further cross-linked by a secondary GAH Ab [], similar to our observations with intact murine 1F5" (col. 1-2, page 6593).

There is no mention of ADCC activity or complement fixation activity in Shan *et al.* other than the statement that both "are dependent on the physical presence of the Fc portion of the Ig molecule" (col. 2, page 6594). Nor is there even a mention of the possibility of 1F5 scFv-Ig ADCC or complement fixation activity, or that any such activities should be tested for.

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[7] See also col. 2, page 6593: "In this study, we have constructed four 1F5 scFv-Ig with different length linker peptides to explore whether the binding of 1F5 scFv-Ig will be affected as reported in other Ab systems."

Those skilled in the art would not have expected such a construct to have ADCC and/or CDC activities. For example, papers published prior to Shan *et al.* reported that a hinge region is required for an IgG to have ADCC and CDC activities. Klein *et al.*, *Proc. Natl. Acad. Sci.* USA 78:524-528 (1981) reported that IgG1 kappa hinge deletion mutants have no ADCC and CDC activity, and that reduction and alkylation of normal IgG hinge disulfides resulted in loss of effector functions. Similarly, with recombinant proteins, deletion of hinge in human IgG3 molecules was reported to result in depressed ADCC levels. Michaelsen *et al.*, *Mol. Immunol.* 29:319-326 (1992); Redpath *et al.*, *Hum. Immunol.* 59:720-727 (1998). This group later wrote, following studies with recombinant human IgG3 antibodies, that "the H chains must be disulfide linked in the N-terminal part of the CH2 domains to create molecules active in effector functions." Michaelsen *et al.*, *Proc. Natl. Acad. Sci.* USA 91:9243-9247 (1994). In 1995 the same group wrote that the "requirement of the hinge region for complement activation is the presence of inter-heavy-chain disulfide bond(s)." Brekke *et al.*, *Immunol. Today* 16:85-90 (1995)). Additionally it was earlier reported that chimeric antibodies expressed with hinge cysteines changed to serines had "greatly reduced" ADCC and "reduced" CDC activities. Gillies *et al.*, *Hum. Antibodies Hybridomas* 1:47-54 (1990). Two years later, these same authors reported that ADCC was "completely abolished" and CDC reduced "fifteen-fold" in the same mutant antibody (Doral *et al.*, *Mol. Immunology* 29:1487-1491 (1992). Studies with conventional IgG molecules showing that the presence of a hinge disulfide bond is necessary for a molecule to have ADCC and CDC functions would lead one to expect that an scFv-Ig molecule with no hinge cysteines as expressed by Shan *et al.* would not mediate ADCC and CDC functions.

Indeed, with regard to potential uses of the 1F5 scFv-Ig constructs, the Shan *et al.* concluded only that (1) apoptosis may be induced as a result of antigen binding by the scFv portion of the molecule (though optimal apoptosis required cross-linking with a second antibody) and that (2) therapy of CD20-expressing B cell malignancies with 1F5 scFv-Ig "radionuclide conjugates" merit further investigation.[8] However, radionuclide conjugation as suggested by Shan *et al.* with regard to use of the scFv constructs, would not be expected to necessarily preserve ADCC and CDC activities. For example, there are exposed aromatic residues in the CH2 and CH3 domains that are thought to be involved in C1q complement binding (Isenman *et al.*, *Biochemistry* 16:233-240 (1977)) that may be derivatized during an oxidative iodine radiolabeling procedure using chloramine T or iodogen. Although alternative methods of radiolabeling by conjugation of amino groups on lysine residues have been published (Smellie *et al.*, *Cancer Res.* 55:5842s-5846s (1995)), these procedures may also affect ADCC and CDC functions by causing conformational changes and altering residues involved in binding to Fc receptors and to complement components. For example, lysines 320 and 322 of the CH2 domain have been shown to be components of the C1q binding site on IgG (Duncan and Winter, *Nature* 322:738-740 (1988)) and lysine 322 was reported to be required for CDC activity of recombinant human IgG3 antibodies (Thommesen *et al.*, *Mol. Immunol.* 37:995-1004 (2000)). Thus, those skilled in the art would have understood that radionuclide labeling, as suggested by Shan *et al.* for use of the scFv constructs, could result in the loss of ADCC or complement fixation activity by the attachment of isotopes to the free amino groups of exposed lysine residues in the CH2CH3 region of the molecule that lead to a loss of Fc receptor binding. See

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[8] The authors also note in their conclusion of page 6594 that a pretargeting strategy with an scFv-streptavidin conjugate "in combination with biotin-90Y secondary reagents" may also merit further investigation. Such a construct would only include an scFv and not a CH2CH3 region, thus eliminating the possibility of ADCC or complement fixation activity.

also Table 1 of Burke *et al.*, "Radioimmunotherapy for Acute Leukemia," *Cancer Control* 9:106-113 (2002).

Antigen binding is also important for effector function. It has been reported that iodination of antibodies can cause loss of antigen binding due to conformational changes from oxidation (Zhorov *et al.*, *Biokhimiia* 56:828-838 (1991)) and to derivation of tyrosine residues involved in binding (Nikula *et al.*, *Mol. Immunol.* 32:865-872 (1995)). In fact, special procedures for antibody conjugation have been created to protect the antigen binding site from damage and to prevent major conformational changes. Van den Abbeele *et al.*, *J. Nucl. Med.* 32:116-122 (1991). It would be expected that antibody conjugation could have a deleterious effect on ADCC and CDC effector functions.

It is the law that, in relying upon inherency to support a rejection, an examiner "must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); *In re King*, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983); *In re Oelrich*, 666 F.2d 578, 212 USPQ 323 (CCPA 1981); *In re Wilding*, 535 F.2d 631, 190 USPQ 59 (CCPA 1976); *Hansgirg v. Kemmer*, 102 F.2d 212, 40 USPQ 665 (CCPA 1939). Inherency means inevitability and it "may not be established by probabilities or possibilities." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Thus, even the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (emphasis added); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). As emphasized by the

court in *In re Oelrich*, an alleged feature of a prior art construct can only be inherent if "the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function" 666 F.2d at 581, 212 USPQ at 326. That is not the case here.

Furthermore, not only must it be established that descriptive matter missing from an alleged reference is necessarily present in the thing described in an alleged reference, case law from the Federal Circuit indicates that in various circumstances it must also be established "that it would be so recognized by persons of ordinary skill." *In re Robertson, supra*; *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). (Fed. Cir. 1991). This recognition requirement has been said to "be sensible for claims that recite limitations of structure, compositions of matter, and method steps which could be inherently found in the prior art." *EMI Group North America, Inc. v. Cypress Semi Conductor Corp.*, 268 F.3d 1342, 1350-1351, 60 USPQ2d 1323, 1429 (Fed. Cir. 2001).[9]

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[9] The court went on to state: "Theoretical mechanisms or rules of natural law that are recited in a claim, that themselves are not patentable, however, do not need to be recognized by one of ordinary skill in the art for a finding of inherency. A person of ordinary skill does not need to recognize that a method or structure behaves according to a law of nature in order to fully and effectively practice the method or structure." *Id.* at 1351, 60 USPQ2d at 1429, citing *e.g.*, *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365, 52 USPQ2d 1303, 1305-06 (Fed. Cir. 1999). The court gave a hypothetical example to clarify the principle: "Humans lit fires for thousands of years before realizing that oxygen is necessary to create and maintain a flame. The first person to discover the necessity of oxygen certainly could not have obtained a valid patent claim for 'a method of making a fire by lighting a flame in the presence of oxygen.' Even if prior art on lighting fires did not disclose the importance of oxygen and one of ordinary skill in the art did not know about the importance of oxygen, understanding this law of nature would not give the discoverer a right to exclude others from practicing the prior art of making fires." *Id.* at 1351, 60 USPQ2d at 1429-1430. See also *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003), not requiring a recognition where the prior art compound held to inherently anticipate was a metabolite that was necessarily formed by the process disclosed in the prior art reference. 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003). Noting that a patent drafter might "fashion a claim" in a way that avoids anticipation, as well as valid claims to pharmaceutical compositions and methods of treatment, the *Schering Corp. v. Geneva Pharm., Inc.*, court further stated: "Continental Can stands for the proposition that inherency, like anticipation, requires a determination of the meaning of the prior art... Thus, in Contential Can, this court did not require past recognition of the inherent feature, but only allowed recourse to opinions of skilled artisans to determine the scope of the prior art reference."

It is also established that to serve as an anticipation when the reference is silent about an asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. That evidence, however, "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Finnigan Corp. v. ITC*, 180 F.3d 1354, 1365, 51 USPQ2d 1001, 1009 (Fed. Cir. 1999) (emphases added); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159, 47 USPQ2d 1829, 1834 (Fed. Cir. 1998). "[E]xtrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference." *In re Baxter Travenol Lab.*, 952 F.2d 388, 390, 21 USPQ2d 1281, 1284 (Fed. Cir. 1991). "For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art ....Although this disclosure requirement presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there." *Motorola, Inc. v. Interdigital Tech Corp.*, 121 F.3d 1461, 1474, 43 USPQ2d 1481, 1490 (Fed. Cir. 1997).

In *Hitzeman v. Rutter*, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001), the Federal Circuit considered whether a party to an interference count was required to show conception of a claim limitation to a particulate form of a protein expressed in yeast and the sedimentation properties of the protein, or whether such a showing was unnecessary because production of the particulate form was inherent when the protein is expressed in yeast. In rejecting a finding of inherency, the Federal Circuit relied on the fact that the inventor, after the patent application was filed, had asserted in a scientific publication that there was uncertainty as to whether the protein particles at issue were formed in the yeast, or whether the particles formed during the purification process after the proteins were extracted from the yeast. *Id.* at 1352, 58 USPQ2d at

1165. The court stated, "consistent with the law of inherent anticipation, an inherent property must necessarily be present in the invention described by the count, and it must be so recognized by persons of ordinary skill in the art."... "Although it may be true in a scientific sense that the yeast 'inherently' produce the claimed particles, that does not mean that the particle size and the sedimentation rate limitations are 'inherent' in a legal sense." *Id.* at 1355, 58 USPQ2d at 1168-1169. In explaining its holding, the court elaborated that "There may be situations where an organism's performance of certain processes might be reasonably predictable, and evidence of such predictability might be sufficient to support a finding of conception prior to reduction to practice. In this case, however, substantial evidence supports the Board's finding that Hitzeman lacked reasonable certainty that the yeast would produce the particles recited in the counts."

The Examiner's conclusion that the Shan *et al.* construct would inherently have "complement fixation or dependent cell-mediated cytotoxicity" cannot stand. There is no indication that this would be the case, or that it would be recognized by persons of ordinary skill (and every indication that those skilled in the art would not). There is no indication that the Shan *et al.* constructs, prepared and used as suggested, would inevitably have ADCC or complement fixation activity. Additionally, it is understood that not only is antigen binding to the variable regions of an immunoglobulin required for ADCC activity, but the binding of antibodies to multiple copies of an antigen is needed.[10] The hinge region is also an important component for ADCC, and changes within the hinge can enhance or inactivate Fc receptor binding and

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[10] See for example, the following excerpt from a basic immunology textbook: "Although many effector functions of antibodies are mediated by the Ig heavy chain constant regions, all these functions are triggered by the binding of antigens to the variable regions. The binding of antibodies to multiple copies of an antigen brings the Fc regions of antibodies close together, and this leads to the complement activation and enhanced interactions of the antibodies with Fc receptors on phagocytes. The requirement for antigen binding ensures that antibodies activate various effector mechanisms only when they are needed, that is, when the antibodies encounter and specifically bind antigens, not when the antibodies are circulating in an antigen-free form." Cellular and Molecular Immunology; Fifth Edition, A.K. Abbas and A.H. Lichtman, 2003, Chapter 14, p. 320 (emphases added).

ADCC.[11] Moreover, the 1F5 scFv polypeptides described in Shan *et al.* are primarily monomeric (see Figures 4 and 5, and discussion in Shan *et al.*). It has been reported in the art that breaking or preventing the formation of disulphide bonds in the lower hinge region would be expected to disrupt dimerization and prevent FcR binding and resulting ADCC. Klein *et al.*, *Proc. Natl. Acad. Sci.* USA 78:524-528 (1981). It has been suggested that functional binding of Fc to FcR requires avidity stabilization of the Fc-FcR complex, such as formation of a dimeric structure of heavy chains as in a conventional antibody or through cross-linking by a conventional Ab Fc structure.

Applying the applicable legal requirements of inherency to the instant circumstance, the Patent Office has not discharged the burden of establishing that the allegedly inherent feature or features necessarily flow from the teachings of the alleged prior art. The focus of Shan *et al.* was to characterize the effect of different linkers in 1F5 scFvs on their ability to bind the target antigen and Shan *et al.* is totally silent regarding ADCC and complement fixation. Applicants respectfully request that the rejection be reconsidered and withdrawn.

***The Second Rejection***

Claims 1-3, 5, 7-11, and 19 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Bodmer *et al.*, U.S. Patent 5,677,425 (May 22, 2003 Office Action, pages 7-8). The Office Action states that Bodmer *et al.* teaches "an antibody wherein the hinge region is modified to have one cysteine and variable regions and the constant regions can be humanized" (May 22, 2003 Office Action at page 7; emphasis added). The Office Action further alleges that "since the hinge has only one cysteine it would be inherent that it would have a reduced ability to dimerize and since the fusion protein has the hinge, CH2 and CH3 it is inherent that the protein has the complement fixation or dependent cell-mediated cytoxicity" (*id.*).

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[11] *E.g.*, Michaelsen *et al.*, *Scand. J. Immunol.* 32:517-528 (1990).

The rejection must be withdrawn because a claim may be rejected for anticipation only if a single prior art reference discloses each and every limitation of the claimed invention, as arranged in the claim. *See Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopedics, Inc.*, 976 F.2d 1559, 1565 (Fed.Cir.1992); *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987); *Lindemann Maschinenfabrik GMBH, v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed.Cir.1984). Bodmer *et al.* does not do so. The Bodmer *et al.* patent is generally directed to complete antibodies and $(Fab')_2$ fragments. It does not disclose any construct of the rejected claims. For example, it does not disclose, expressly or inherently, a molecule having a binding domain polypeptide coupled to one of hinge molecules (i) - (v) coupled to CH2CH3. The Office Action is silent regarding the fact that Bodmer *et al.* fails to teach or suggest a single chain polypeptide or a polypeptide without a CH1 domain, and the . Bodmer *et al.* patent makes repeated reference to a molecule that includes a CH1 region (see for example at column 3, lines 13-17; column 3, lines 46-50; column 4, lines 28-35; column 6, lines 52-56; column 8, lines 1-3; column 8, lines 26-34). The anticipation rejection cannot stand and Applicants respectfully request that it be reconsidered and withdrawn.

***The Third Rejection***

Claims 1, 3, 8, 12, and 19 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Morrison *et al.*, U.S. Patent 6,284,534 (May 22, 2003 Office Action, page 8). The Office Action states that Morrison "teaches an antibody that has an IgA hinge" and that, "since the antibody has the hinge, CH2, and CH3 it is inherent that the protein has complement fixation or dependent cell-mediated cytotoxity" (emphases added). As with Bodmer *et al.*, the Morrison *et al.* '534 patent does not teach a molecule having a binding domain polypeptide coupled to one of hinge molecules (i) - (v) coupled to CH2CH3. The Office Action is silent regarding the fact that

Morrison *et al.* fails to teach or suggest a single chain polypeptide or a polypeptide without a CH1 domain. Because a claim may be rejected for anticipation only if a single prior art reference discloses each and every limitation of the claimed invention, as arranged in the claim, Applicants respectfully request that the rejection be withdrawn. As a matter of law, Morrison *et al.* does not anticipate the claimed inventions.

**35 U.S.C. §103(a)**

***Legal Requirements Relating to Nonobviousness***

A claimed invention may be rejected as unpatentably obvious only if it can be shown that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. Section 103(a) (1994). Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the ordinary artisan, and objective considerations. *E.g., Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

To establish a *prima facie* case of obviousness based on a combination of the content of various alleged references, there must be some objective teaching, suggestion or motivation in the prior art to make the specific combination. *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). The teachings of the alleged references, their relatedness to the field of the applicant's endeavor, and the knowledge of persons of ordinary skill in the field of the invention, are all relevant considerations. *See In re Oetiker*, 977 F.2d at 1447, 24 USPQ2d at 1445-46; *In re Gorman*, 933 F.2d at 986-87, 18 USPQ2d at 1888; *In re Young*, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). Thus, there is no suggestion that would support a

conclusion of obviousness within the meaning of 35 U.S.C. 103 if an alleged reference teaches away from the invention, or from its combination with another source. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant . . . [or] if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Additionally, obviousness can not be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As discussed in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the alleged prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."). It has been held that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine any alleged prior art references.

An obviousness rejection cannot be supported by the mere statement that a particular property is inherent. "Inherency and obviousness are distinct concepts." *W.L. Gore & Associates, Inc. v. Garlock, Inc.* 721 F.2d 1540, 1555, 220 USPQ 303, 314 (Fed. Cir. 1983) (citing *In re Spormann*, 363 F.2d 444, 448 150 USPQ 449, 452 (C.C.P.A. 1966)). "That which

may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown". *In re Spormann*, 363 F.2d 444, 448 150 USPQ 449, 452 (C.C.P.A. 1966). A retrospective view of inherency is not a substitute for some teaching or suggestion that supports an obviousness rejection. *In re Newell*, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).

***The First Rejection***

Claims 1-11 and 19 were rejected under 35 U.S.C. § 103 as allegedly unpatentable over Shan *et al.* in view of Bodmer *et al.* (May 22, 2004 Office Action, pages 9-10). The Examiner acknowledges that "Shan et al does not teach a mutated hinge containing one cysteine or a variable region from a human immunoglobulin" (*id.*, page 9).

The Office Action alleges, however, that Bodmer *et al.* "teach mutations to reduce cysteines in the hinge have the advantage that it will facilitate assembly of the antibody molecules" (*id.*), and concludes that "it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the hinge region of Bodmer et al in the construct of Shan et al" (*id.*, page 10). The Office Action alleges that "one of ordinary skill in the art would have been motivated to and has a reasonable expectation of success to have used the hinge region of Bodmer et al in the construct of Shan et al" because (1) "Shan et al teach that they are focusing on making antibodies that are bivalent" and (2) Bodmer et al teach reducing the cysteine residues in the hinge to one facilitates assembly of the antibody molecules." The Office Action concludes that "it would have been obvious to one of ordinary skill to have used the hinge region of Bodmer et al which has a single cysteine residue and substitute this hinge for the hinge in Shan et al in order to produce an antibody which had the affinity of an intact antibody because it would have two binding sites" (*id.*).

A conclusion that Shan *et al.* suggests a modification of the hinge region to produce bivalent antibodies is incorrect. First, Applicants note that the statement that "Shan et al teach that they are focusing on making antibodies that are bivalent" is inconsistent with the prior statement in the Office Action that the molecules described in Shan *et al.* "can not dimerize" because all the cysteines are removed (May 22, 2004 Office Action, page 7). Second, there is no discussion in Shan *et al.* regarding a desire to modify the hinge region to have cysteine residues capable of forming a disulfide bond to make a bivalent polypeptide. The last sentence of Shan *et al.*, which refers to some unidentified potential structural modifications that may "generate dimeric scFv," must be read in the context of the entire article. The focus of the Shan *et al.* publication is identified in its title, "Characterization of scFv-Ig Constructs Generated from the Anti-CD20 mAb 1F5 Using Linker Peptides of Varying Lengths." (Emphasis added.) This is supported throughout the text of Shan *et al.* See, for example, the following passage discussing the incongruity that "most of the functionally active 1F5 scFv-Ig were monomeric despite the differences in their linker peptide lengths" (page 6594, left column, first sentence of the last full paragraph): "One potential explanation for the apparent increase in the CD20 binding activity of the 1F5 scFv-Ig constructs synthesized with the shorter linkers peptides may be that they formed dimers or multimers in culture, leading to an increase in their binding valency." In contrast to the statements in the Office Action, Shan *et al.* contains no explicit discussion regarding any modification of cysteines in a hinge region to generate a dimeric scFv. There is no motivation to combine the disclosure of Shan *et al.* regarding a molecule with no CH1 domain with a document relating to whole antibodies and antibody $(Fab')_2$ fragments.

The Office Action also characterizes Bodmer *et al.* as follows, stating that, "Since the hinge has only one cysteine it would be inherent that it would have a reduced ability to dimerize"

(emphasis added). However, Bodmer *et al.* specifically states that use of one cysteine will "facilitate" dimerization, not reduce it. See, for example, col. 3, lines 60-66, of the Bodmer *et al.* '425 patent, where it is stated that reduction of the number of cysteines to one "will facilitate assembly of the antibody molecules, particularly bispecific antibody molecules and antibody molecules wherein the Fc portion has been replaced by an effector or reporter molecule, since it will only be necessary to form a single disulfide bond" (emphasis added). In other words, Bodmer *et al.* is directed to use of a single cysteine to prevent mismatching when constructing a bi-specific antibody or one that can have no ADCC or CCD effector function at all, *i.e.*, a molecule that has no Fc region.

Shan *et al.* and Bodmer *et al.* are quite different and there is no basis to combine them. The first is directed to linker lengths between the $V_H$ and $V_L$ in an scFv peptide having one antigen binding site and no hinge cysteines. The second is directed to altered antibody and $(Fab')_2$ molecules having two antigen binding sites and an increased or decreased number of hinge cysteines "capable of forming a heavy chain to heavy chain disulfide bond," said to be useful for constructing bi-specific antibody and $(Fab')_2$ molecules or molecules that have no ADCC or CCD effector function. It is submitted that one of skill in the art would not be motivated to combine the two documents, let alone attempt to combine them in an effort to produce the instant clamed molecules having ADCC or CCD effector function. Applicants respectfully request that the rejection be reconsidered and withdrawn.

***The Second Rejection***

Claims 1-12 and 19 were rejected under 35 U.S.C. § 103 as allegedly unpatentable over Shan *et al.* in view of Bodmer *et al.* and Morrison *et al.* (May 22, 2004 Office Action, pages 10-12).

The Office Action acknowledges that Shan *et al.* does not teach "a mutated hinge region containing one cysteine or a IgA hinge or mutated IgA hinge or a variable region from a human immunoglobulin" (*id.*, page 11). The Office Action alleges, however, that Bodmer *et al.* "teach mutations to reduce cysteines in the hinge have the advantage that it will facilitate assembly of the antibody molecules (see column 3, lines 60-73)" (*id.*), that "Morrison et al teaches an antibody that has an IgA hinge" (*id.*), and that "it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the hinge region of Morrison et al or mutate the hinge regions as taught by Bodmer et al in the construct of Shan et al" (1) because "Shan et al teach that they are focusing on making antibodies that are bivalent," (2) because "Bodmer et al teach reducing the cysteine residues in the hinge to one facilitates assembly of antibody molecules," and (3) because "Morrison et al teach the benefits of and IgA Fc and specifically and IgA with a hinge region" (*id.*). The Office Action further alleges that "it would have been obvious to one of ordinary skill in the art to have used the hinge region of Morrison et al or mutate the IgA hinge region as taught by Bodmer et al which has a single cysteine residue and substitute this hinge for the hinge in Shan et al in order to produce an antibody which had the affinity of an intact antibody because it would have two binding sites" (May 22, 2004 Office Action, pages 10-12).

The addition of Morrison *et al.* to the previous rejection of claims over Shan *et al.* in view of Bodmer *et al.* does not save the rejection and Applicants respectfully request that it be reconsidered and withdrawn.

The Office Action asserts at page 11 that one would have been motivated to use the "hinge region of Morrison" because Shan is *et al.* "focusing on making antibodies that are bivalent." This conclusion is not supported by either Shan *et al.* or Morrison *et al.* Applicants

assume that use of the term "bivalent" in the Office Action is a reference to page 6594 in Shan *et al.* where the authors note that an apparent increase in "binding activity" may be a result of "dimer" formation. Such alleged "bivalency", however, is related to linker engineering and has nothing to do with hinge engineering. Additionally, the argument is a *non sequitor* because there is no connection between an IgA hinge and bivalency. Indeed, Morrison *et al.* contains no particular disclosures about hinges other than the following five statements, four of which are generic and not specifically related to the described subject matter (all emphases added):

1. The statement in the "Detailed Description of the Invention" (under "Definitions") that, "As used herein, 'constant region domain' or 'constant domain' refers to a domain within the constant portion of an Ig molecule, including $C_L$, $C_H1$, hinge, $C_H2$, $C_H3$ and $C_H4$.";
2. The statement in the "Detailed Description of the Invention" (under "Modified Immunoglobulin Molecule") that, "The present invention provides a modified immunoglobulin molecule comprising a constant domain of an IgA molecule, and at least a portion of a nonIgA immunoglobulin molecule. Examples of a constant domain of an IgA molecule include, but are not limited to, $C_H1(C\alpha1)$, hinge, $C_H2(C\alpha2)$, and $C_H3(C\alpha3)$.";
3. The statement in the "Detailed Description of the Invention" (under "Modified Immunoglobulin Molecule") that, "constant region domains, such as hinge, $C_H2$, $C_H3$ and $C_H4$, possess functional or biological features which are characteristic of these particular domains.";
4. The statement in Example 1 (under " Results - Generation and Expression of $\alpha.1/\gamma2$ Exon Exchanged Genes") that, "With the hinge and $C_H2$ considered as a single unit,

the six possible combinations of α.1/γ2 exon exchanged hybrid genes were generated (FIG. 1B, constructs 1-6).";

5. The statement in Example 3 (under "In Vivo Half-Life") that, "Upon binding to specific antigens, antibodies interact through their Fc regions with both cellular and soluble effector systems. Despite their similar structure, different human IgG isotypes display differences in the ability to perform effector functions, and these differences are attributed mainly to differences in the lower hinge- $C_H2$ regions. Extensive studies have localized the binding sites on IgG for C1q and Fc receptors to the $C_H2$ region (Tan, L. K. et al., 1990, PNAS, USA 87(1):162-6; Duncan, A. R., and Winter, G., 1988, Nature 332(6166):738-40). The removal of N-linked carbohydrate from $C_H2$ in wild type monomeric IgG1 and IgG3 results in decreased C1q binding and the elimination of C' activation and recognition by Fc receptors (Tao, M. H., and Morrison, S. L., 1989, J. Immunol. 143(8):2595-601); Coloma, M. J. et al., 1997, J. Immunol. 158(2):733-40; Walker, M. R. et al., 1989, Biochem. J. 259(2):347-53)."

There is no suggestion or motivation in either Shan *et al.* or Morrison *et al.* to include an IgA hinge (modified or otherwise) in the Shan *et al.* construct.

The Office Action further asserts at page 12 that one would have been motivated to use the "hinge region of Morrison" because Morrison *et al.* "teach the benefits of an IgA Fc and specifically an IgA with a hinge region." Although it is not understood what "benefits" are meant by this statement, it is not believed that Morrison *et al.* contains such a teaching. Morrison *et al.* says nothing about benefits of an IgA hinge or an IgA Fc with regard to ADCC and/or CDC. Additionally, the statement does not have meaning in relation to Applicants' inventions, which does not relate to whole antibodies.

Applicants respectfully request that the rejection be reconsidered and withdrawn.

**The Third Rejection**

All pending claims 1-14 and 19 were rejected under 35 U.S.C. § 103 as allegedly unpatentable over Shan *et al.* in view of Bodmer *et al.*, Morrison *et al.*, and Armitage *et al.*, U.S. Patent 6,264,951 (May 22, 2004 Office Action, pages 12-14).

The Office Action acknowledges that Shan *et al.* "does not teach a mutated hinge region containing one cysteine or a IgA hinge or mutated IgA hinge or a variable region from a human immunoglobulin or the extracellular domain of CD154 or a fusion protein of CD154 and an immunoglobulin domain" (*id.*, pages 12-13). The Office Action alleges, however, that Bodmer *et al.* "teach mutations to reduce cysteines in the hinge have the advantage that it will facilitate assembly of the antibody molecules (see column 3, lines 60-73)" (*id.*, page 12), that "Morrison et al teach an antibody that has an IgA hinge" (*id.*), and that Armitage *et al.* teaches a "CD154 (CD40L) fused to an Fc and divalent CD40L fusions to heavy and lights chains of antibodies to form oligomers (see column 7-10)." It is concluded in the Office Action that "it would have been prima facie obvious . . . to have used the hinge region of Morrison et al or the mutant hinge regions taught by Bodmer et al in the construct of Shan et al and fuse the extracellular domain of CD154 to the construct" because, it is alleged, "Shan et al teach that they are focusing on making antibodies that are bivalent," "Bodmer et al teach reducing the cysteine residues in the hinge to one facilitates assembly of antibody molecules," "Morrison et al teach the benefits of an IgA Fc and specifically an IgA with a hinge," and "Armitage et al teach oligomers of CD40L are made with both heavy and light chains of the antibodies and form oligomers" (*id.*).

The addition of Armitage *et al.* to the previous rejection of claims over Shan *et al.* in view of Bodmer *et al.* and Morrison *et al.* does not save the rejection and Applicants respectfully request that it be reconsidered and withdrawn.

Armitage *et al.* does not provide the suggestion or motivation alleged in the Office Action. As noted in the "Detailed Description of the Invention" in the Armitage *et al.* patent the primary structure of CD40-L may be modified to create CD40-L "derivatives." Such derivatives are identified as "CD40-L polypeptide fusions" that "can comprise polypeptides added to facilitate purification and identification of CD40-L (e.g. poly-His), or fusions with other cytokines to provide novel polyfunctional entities." These "other cytokines" are said to include any of "interleukins-1 through 13, TNF (tumor necrosis factor), GM-CSF (granulocyte macrophage-colony stimulating factor), G-CSF (granulocyte-colony stimulating factor), MGF (mast cell growth factor), EGF (epidermal growth factor), PDGF (platelet-derived growth factor), NGF (nerve growth factor), EPO (erythropoietin), .gamma.-IFN (gamma interferon), 4-1BB-L (4-1BB ligand) and other cytokines that affect immune cell growth, differentiation or function." Additionally, Armitage *et al.* specifically discuss the creation of oligomers, such as "dimers or trimers", that are linked by disulfide bonds, as well as the creation of oligomers with as many as four CD40-L extracellular regions." According to the Armitage *et al.* patent:

> CD40-L polypeptides may exist as oligomers, such as dimers or trimers. Oligomers are linked by disulfide bonds formed between cysteine residues on different CD40-L polypeptides. Alternatively, one can link two soluble CD40-L domains with a Gly.sub.4 SerGly.sub.5 Ser linker sequence, or other linker sequence described in U.S. Pat. No. 5,073,627, which is incorporated by reference herein. CD40-L polypeptides may also be created by fusion of the C terminal of soluble CD40-L (extracellular domain) to the Fc region of IgG1 (for example, SEQ ID NO:3) as described for the CD40/Fc fusion protein. CD40-L/Fc fusion proteins are allowed to assemble much like heavy chains of an antibody molecule to form divalent CD40-L. If fusion proteins are made with both heavy and light chains of an antibody, it is possible to form a CD40-L oligomer with as many as four CD40-L extracellular regions.

This does not support a conclusion of obviousness of the claimed inventions.

Furthermore, Armitage *et al.* contains nothing about hinges other than the following three statements (all emphases added):

1. The statement in the "Detailed Description of the Invention" that, "The PCR amplified cDNA introduced a Bgl II site near the beginning of the hinge region, which was used to ligate CD40 extracellular domain to construct as CD40/Fc fusion cDNA, which was ligated into pDC406 to construct pDC406/CD40/Fc.";
2. The statement in the "Detailed Description of the Invention" that, "Glu and Pro are the first two amino acids of a hinge region of human IgG1, and are followed by a Bgl II restriction site. The Bgl II restriction site was used to fuse the extracellular domain of CD40 to the remainder of human IgG1 Fc region."; and,
3. The statement in Example 1 that, "Glu and Pro are the first two amino acids of a hinge region of human IgG1, and are followed by a Bgl II restriction site that was used to fuse the extracellular domain of CD40 to the remained of human IgG1 Fc region."

Applicants respectfully request that the rejection be reconsidered and withdrawn.

## CONCLUSION

In conclusion, Applicants respectfully submit that all pending claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned Representative if it is believed that prosecution may be furthered thereby.

Respectfully Submitted

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